Scottish Paediatric Endocrine Network (SPEG)

Guideline for Investigation of early (precocious) and late (delayed) puberty in girls and boys

NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Quick Reference Guide

Who to refer to secondary care: Precocious (early) Puberty

Boys <9 years	Girls < 8 years
Increased testicular volume (≥4ml) and/or virilisation of genitalia (penile growth)	Breast development Virilisation of external genitalia (clitoromegaly)
Accelerated height growth	Accelerated height growth
	Excessive tall stature
	Menarche (Before age 10 years)

*Note development of pubic/axillary hair, body odour, skin oiliness and acne without signs of central puberty (those described in the table above) is called **Adrenarche**. This can be a normal variant. Please see the Adrenarche guideline for further information and referral criteria

Who to refer to secondary care: Delayed Puberty

Boys ≥14 years	Girls ≥13 years
No increase in testicular volume (< 4mls)	No breast development
No accelerated height growth (may not occur until potentially 16yrs when testicular volume 10 mls + but if psychologically distressed can see pre age 14/16 yrs)	No accelerated height growth Short stature for family
Short stature for family	No menarche within 3 years of onset of puberty (by age 15 years latest)

Key information to include in the referral:

- growth history with the height at the time of referral and previous height measurements if available
- parental heights
- family history of early or delayed puberty
- assessment of any androgen-dependent characteristics e.g. axillary/pubic hair, clitoromegaly, penile growth
- any other medical problems. Many chronic health conditions can lead to pubertal delay
- any concerns about pathological cause e.g., space occupying lesion

Investigations:

Baseline investigations can be arranged by the referring clinician. These should be interpreted in the clinical context and therefore if a patient has clinical signs of precocious puberty, but normal tests (low LH/FSH/oestradiol) referral is still appropriate as further investigation may be required. Referrals should be routine unless there are concerns about pathological cause, for example space occupying lesion.

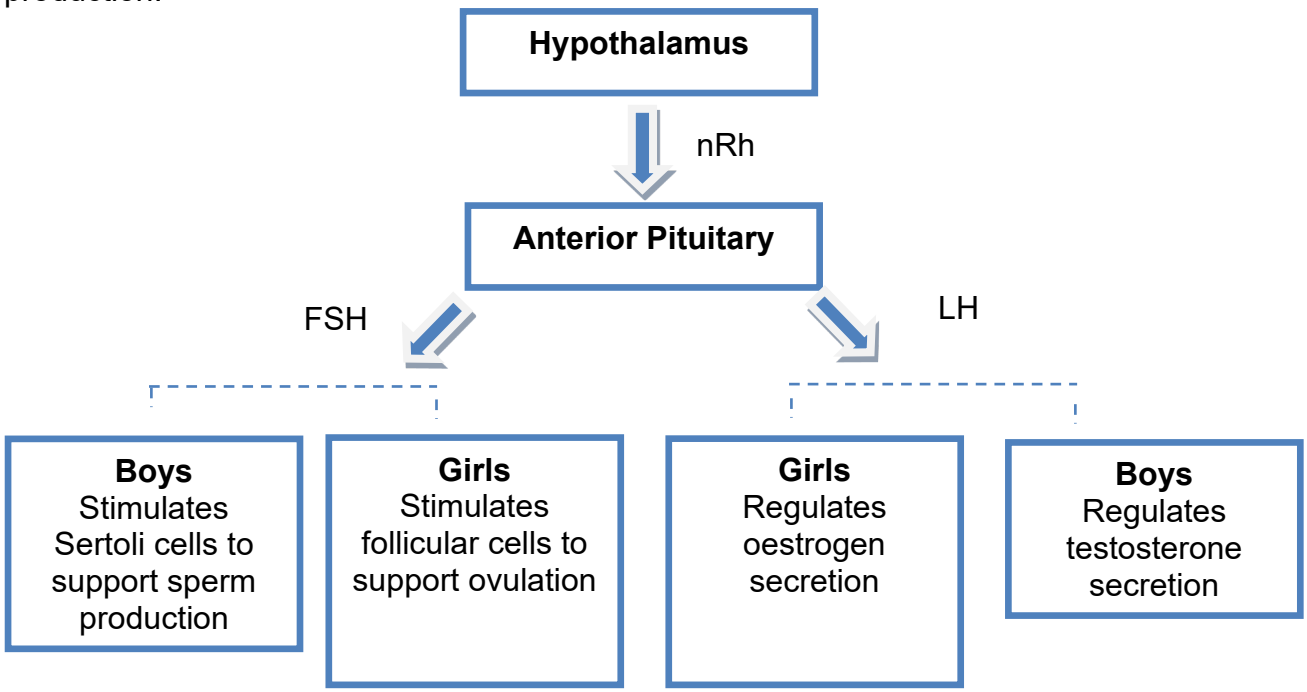
- blood tests: FSH, LH, testosterone/oestradiol, TSH, fT4
- coeliac screen if symptoms suggestive of this
- full blood count, CRP/ESR if delayed puberty (IBD may present with delayed puberty)
- bone age x-ray
- pelvic USS (girls): request ovarian and uterine volume

Introduction

Puberty is the stage of development in boys and girls which involves:

1. Maturation of the gonads
2. Increase in the secretion of sex hormones
3. Accelerated linear growth
4. Development of secondary sexual characteristics

Puberty is controlled centrally by the pituitary gland via the **hypothalamic-pituitary-gonadal axis**. In girls LH and FSH stimulate maturation of the ovaries and secretion of oestradiol, whilst in boys they stimulate testicular maturation and testosterone production.



Oestrogen and testosterone are the key players in the pubertal growth spurt. They work directly on the growth plate to stimulate growth. Oestrogen (from the ovary or aromatised testosterone from the testes) contributes to an increase in response to growth hormone during puberty.

The pituitary also stimulates the adrenal glands to produce androgens. This process occurs independently of the pituitary-gonadal axis. If this process occurs in isolation, it is called **Adrenarche** and results in the development of pubic/axillary hair, body odour, skin oiliness and acne without signs of central puberty. This can be a normal variant. Please see the separate Adrenarche guideline on RefHelp for further information.

Normal Patterns of Puberty

In girls the first sign of puberty is breast development (breast buds). This is usually followed by accelerated linear growth in early to mid-puberty (growth spurt). Menarche usually signals the end of pubertal development. Androgen dependent characteristics (axillary hair, pubic hair, acne, oily skin etc) usually develop in mid-puberty.

In boys the first sign of puberty is an increase in testicular volume. As in girls, androgen dependent characteristics usually develop in mid-puberty. Accelerated linear growth occurs in mid to late puberty in boys.

Girls and boys have different ages at which pubertal development is considered to be normal. Early (precocious) or delayed puberty is defined as the presence or absence of pubertal signs before or after the following ages.

	Boy	**Girl**
Early Puberty	<9 years	<8 years
Delayed Puberty	≥14 years	≥13 years

Puberty is normally completed in 2-5 years.

Precocious (early) Puberty

Signs of puberty in girls <8 years of age and boys <9 years of age are indicative of precocious puberty.

Boys < 9 years	Girls < 8 years
Increased testicular volume (≥4ml)	Breast development
Accelerated linear growth	Accelerated linear growth
Tall stature	Tall stature
	Menarche

There are two types of Precocious Puberty:

- **Gonadotrophin- Dependent (Central) Precocious Puberty**

  This is the most common type and results from premature activation of the hypothalamo-pituitary-gonadal axis. The pattern of pubertal development follows that of normal puberty.

- **Gonadotrophin-Independent Precocious Puberty**

  This results from excess peripheral production of sex steroids. Pubertal development does not follow the normal pattern of puberty.

Key Fact
Central Precocious Puberty is more common in girls:
- Girls are more likely to have the idiopathic form (90% of cases)
- Boys are more likely to have an underlying pathological cause (90% of cases)

History	Examination- Girls	Examination- Boys
• Onset of secondary sexual characteristics (and is pattern of development the same as normal puberty) • Rate of development • Recent growth • Parental heights • Parental pubertal history • History of adoption • Medication history	• Height- plot on growth chart • Height velocity • Breast development • Androgen-dependent characteristics • Neurological examination (including fundoscopy to exclude raised ICP) • Dysmorphic features (including skin examination for: café-au-lait spots/ freckles/neurofibromas)*	• Height- plot on growth chart • Height velocity • Testicular volume • Androgen-dependent characteristics • Neurological examination (including fundoscopy to exclude raised ICP) • Dysmorphic features (including skin examination for: café-au-lait spots/ freckles/ neurofibromas)*

*May reveal multisystem syndrome- midline defects, McCune-Albright Syndrome, Neurofibromatosis

Differential	Growth/pubertal Signs	Signs of Adrenarche	Biochemistry	Bone Age	Presenting age	Refer?
Central precocious Puberty	**Girls**- Breast development, increased HV **Boys**- TV ≥4ml Accelerated linear growth, only if TV > 10ml	Yes	↑LH + FSH ↑Sex steroids (although can be normal at baseline)	Advanced	**Girls**: <8 years **Boys**:< 9 years	**Yes**
Premature Adrenarche	No (minimal increase in HV)	Yes	Gonadotrophins- prepubertal Mildly increased androgens		Typically, girls	Not always (see separate guideline)
Premature Thelarche (girls only)	Isolated breast development Often fluctuates	No	Prepubertal LH (<0.5) FSH sometimes slightly raised	Not advanced	6 months- 3 years	Yes
Premature Thelarche Variant (girls only)	Breast development- persistent	Not initially- may progress to central precocious puberty	↑ FSH ?LH may be raised	Not advanced unless progresses to central precocious puberty	Older age of onset >2 years	Only refer if worried features e.g. increased height velocity
Gonadal Tumours: Can secrete oestrogen or testosterone	Disconsonant*	Yes	↑ Sex steroids ↓ LH +/-FSH	Advanced	Variable	Yes

Differential	Growth/pubertal Signs	Signs of Adrenarche	Biochemistry	Bone Age	Presenting age	Refer?
Congenital Adrenal Hyperplasia	Disconsonant*		Raised adrenal hormone precursors	Advanced	Variable	Yes
Adrenal Tumours: Can secrete oestrogen or testosterone	No breast budding (will be present if tumour oestrogen-secreting)/ testicular enlargement Accelerated linear growth	Virilisation	Urine steroid profile- abnormal pattern Raised androgens and/or sex steroids	Advanced	Variable	Yes
Primary Hypothyroidism	Breast budding Testicular enlargement No increase in height velocity	No	↑ TSH	Delayed	Variable	Yes

*Increased height velocity, advanced bone age and advanced genital maturation in the absence of bilateral testicular enlargement in boys and enlargement of ovaries in girls (breast development if tumours are oestradiol/testosterone producing). **Unilateral gonadal enlargement should always be considered as a pathological sign**.
HV = height velocity, TV = testicular volume

Initial Investigations (could be performed at time of referral to endocrinology team or in secondary/tertiary care **but do not delay referral for results if signs in keeping with precocious puberty**):

1. Bone age x-ray
2. Gonadotrophins (LH/FSH)
3. Oestradiol / testosterone
4. Thyroid function tests (TSH/fT4)

Further investigations in central precocious puberty, guided by initial investigations and examination findings:

1. Pelvic ultrasound scan (girls)
2. MRI Brain- in all boys age <9 years and in girls presenting at <6 years of age or with features suggestive of pathological cause (e.g. symptoms of raised intracranial pressure)
3. Adrenal androgen profile (17OHP, androstenedione, DHEAS, testosterone)
4. GnRH Test (if clear signs of puberty in girls e.g. accelerated growth velocity)
5. Other pituitary hormones (cortisol, prolactin, IGF-1)

Delayed Puberty

No signs of central puberty in girls ≥13 years of age and boys ≥14 years of age is indicative of delayed pubertal development.

Key Facts
Delayed puberty is more common in boys.
The majority of patients seek medical advice due to concern about growth rather than pubertal development.

Mechanisms of delay in puberty:

- Functional:
  - Constitutional delay (most common cause, particularly in boys)
  - Underlying chronic disease
  - Malnutrition
  - Excessive exercise
- Hypothalamic-pituitary disorders
  - Hypogonadotrophic hypogonadism
- Gonadal Disorders
  - Hypergonadotrophic hypogonadism

History	Examination
• Chronic medical conditions (e.g. coeliac, inflammatory bowel disease, thyroid disease, inflammatory disorders such as JIA) • Eating pattern/diet/weight loss • Parental pubertal history/height • Previous surgery/radiotherapy to the brain • Boys- testicular pain/swelling/inflammation • Other hormone deficits (hypothyroid etc) • Sense of smell (Kallmann Syndrome*)	• Height and weight and plot on growth chart (+ previous measurements if available) • Signs of chronic medical conditions • Pubertal stage (girls- breast development, boys- testicular volume, both- androgen characteristics) • Neurological examination, including visual field assessment • Body disproportion (tall stature with greater lower limb length in Klinefelter Syndrome*) • Dysmorphic features- Turner Syndrome, midline defects, Prader-Willi, CHARGE)

*Associated with normal or tall stature as opposed to other causes of delayed puberty

Differential	Presenting Sign	Signs of Adrenarche	Investigations	Bone Age	Refer?
Constitutional Delay (most common)	Short stature No secondary sexual characteristics Family history of delayed puberty	Yes/No	Pre-pubertal: LH/FSH + Sex steroids Observation	Delayed	Yes
Hypogonadotropic hypogonadism	Short stature No pubertal development/delay in pubertal development/arrest of pubertal development Anosmia (in Kallmann Syndrome)	No	↓ LH +/-FSH ↓ Sex steroids MRI head DSD Gene panel Pituitary function	Delayed	Yes
Premature Ovarian Failure	Primary amenorrhoea	Yes	↑ LH +/-FSH ↓ Sex steroids AMH Ovarian antibodies Karyotype (for Turner Syndrome) Genes for fragile X (FMR1)	Delayed	Yes
Premature Testicular Failure	May have had normal pubertal development and then pubertal arrest	Yes	↑ LH/FSH ↓Sex steroids Karyotype (for XXY or variants)	Delayed	Yes
Hypothyroidism	Lethargy, cold intolerance, constipation, weight	Yes	Normal LH Thyroid function (TSH/fT4)	Delayed	Yes

Differential	Presenting Sign	Signs of Adrenarche	Investigations	Bone Age	Refer?
	gain, menstrual irregularities				
PCOS	Obesity, hirsutism, acne, weight gain, oily skin. Anovulation- irregular/ absent menarche	Yes	↑ DHEAS ↕ SHBG ↑ Testosterone ↑ Androstenedione	Normal	Yes
Complete Androgen Insensitivity	Phenotypic female- normal breast development No menarche	No	Karyotype: 46XY Pelvic USS- testes, no ovaries/uterus	Normal	Yes
5-alpha Reductase Deficiency	Boys- ambiguous genitalia at birth Development of male secondary sexual characteristics at puberty	No	hCG Test (Testosterone:DHT ratio) Genetics	Normal	Yes
Anatomical (imperforate hymen, absent uterus)	Primary amenorrhoea Other secondary sexual characteristics present	Yes	Pubertal LH, FSH + oestrogen Pelvic USS	Normal	Yes

Initial Investigations (could be performed at time of referral to endocrinology team or in secondary/tertiary care):

1. Bone age x-ray
2. Gonadotrophins (LH/FSH)
3. Oestradiol / testosterone
4. SHBG
5. Thyroid function tests (TSH/fT4)
6. Cortisol
7. Prolactin
8. Pelvic ultrasound scan (females)

Additional investigations if concerned about underlying chronic illness

1. Coeliac screen
2. Faecal calprotectin

Further Reading

Maione L, Bouvattier C, Kaiser UB. Central precocious puberty: Recent advances in understanding the aetiology and in the clinical approach. *Clin Endocrinol (Oxf)*. 2021; 95: 542–555. https:/doi.org/10.1111/cen.14475

Howard SR. Interpretation of reproductive hormones before, during and after the pubertal transition—Identifying health and disordered puberty**.** Clin Endocrinol (Oxf). 2021 Nov; 95(5): 702–715. doi: 10.1111/cen.14578